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PRINTING TECHNIQUES: RECENT DEVELOPMENTS IN PHARMACEUTICAL TECHNOLOGY

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Abstract: In the last few years there has been a huge progress in a development of printing techniques and their application in pharmaceutical sciences and particularly in the pharmaceutical technology. The variety of printing methods makes it necessary to systemize them, explain the principles of operation, and specify the possibilities of their use in pharmaceutical technology. This paper aims to review the printing techniques used in a drug development process. The growing interest in 2D and 3D printing methods results in continuously increasing number of scientific papers. Introduction of the first printed drug Spritam® to the market seems to be a milestone of the 3D printing development. Thus, a particular aim of this review is to show the latest achievements of the researchers in the field of the printing medicines.

Keywords: 3D printing, 2D printing, fused deposition modelling, orodispersible dosage forms, personalized medicines

The achievements of drug development during last decades have been greater than ever before. The new concepts of the dosage forms design and innovation of manufacturing technology have a strong influence on the pharmaceutical development of new drugs. Over the years, various technologies have been developed to achieve the formulation with predefined properties, from the conventional to the modified release dosage forms. Quality of the dosage forms should be build in the drug product based on the understanding of many aspects related to the physical, chemical and biopharmaceutical properties of the active pharmaceutical ingredients (APIs), excipients properties and manufacturing processes GMP. Due to the modernized GMP regulations, understanding of the factors that influence the pharmaceutical product quality is of great importance to successful production.

Novel approaches are proposed especially for dosage forms suitable for defined population, from children to elderly patients. Therefore, recently personalized medicine is challenging study area, and different concepts for individualized therapy are proposed. The dosing precision of drug formulations ensure effectiveness in safe drug therapy. The most valuable strategy concerns dosage forms with high dose flexibility and low production costs.

Recently, considerable attention has been focused on manufacturing methods of novel dosage forms with usage of different types of printers. Three-dimensional (3D)- or two-dimensional (2D)-printing is rapidly developing. The first 3D-printed levetiracetam orodispersible tablets (Spritam®) was approved by FDA. It is emphasized that highly precise ratio of the active ingredient to excipients can be achieved in controlled manner.

The aim of the paper is to review the usage of printing techniques in pharmaceutical technology.

Three dimensional printing methods

The term "3D printing" is related to the numerous methods of rapid prototyping, that are used in a process of new product development, making it less expensive and less time consuming. 3D printing is defined by International Standard Organization (ISO) as: "fabrication of objects through the deposition of a material using a print head, nozzle, or another printer technology" (1) and could be referred to a solid freeform fabrication (SFF) or additive manufacturing (AM), i.e. a process of forming 3D objects layer-by-layer by

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addition and solidification of raw materials without using molds or casts (2).

Development of 3D printed objects includes several steps common for different printing techniques (Fig. 1) (3).

- Construction of 3D object with computer-aided design (CAD) software. During this phase the printing method and properties of the printer (e.g. resolution) should be taken into account.
- Export of 3D model to STL file format, compatible with 3D printer. The STL format, which is an abbreviation coming from STereoLithography was originally developed by 3D Systems company as a native format for their first stereolithography printer commercialized in 1989 (4). STL files describe triangulated surface geometry of 3D object, and are currently used not only in the stereolithography, but also in other 3D printing methods.
- Import of the STL file to the printer software, and if necessary, generation of supports to prevent object collapsing. Printing program slices 3D model into layers corresponding to printed layers, and data is transferred as XYZ coordinates to the printer.
- Layer-by-layer building of object by solidification of different raw materials dependent of the used 3D printing method.
- Sometimes, additional post processing steps, such as drying, smoothing, and removing of supports or residual powder are performed.

There are several 3D printing methods with different object building systems based on:

- ink solidification or ink binding of a free powder,
- solidification of a photopolymer in the presence of light,
- extrusion of material – fused deposition modeling (FDM) or syringe pressure systems, that can be used in the area of drug delivery development (Fig. 2) (5).

The first 3D printing method used for the development of pharmaceutical dosage forms was deposition of ink on the powder bed – drop on solid deposition (DoS). Droplets of ink with defined diameter are sprayed by print head on a surface of free powder, where they bind its particles into layer, whereas unbound powder is used as a scaffolding for overhang faces or porous structures. First print heads used in this process were commercially available heads from inkjet printers. Droplets of ink are

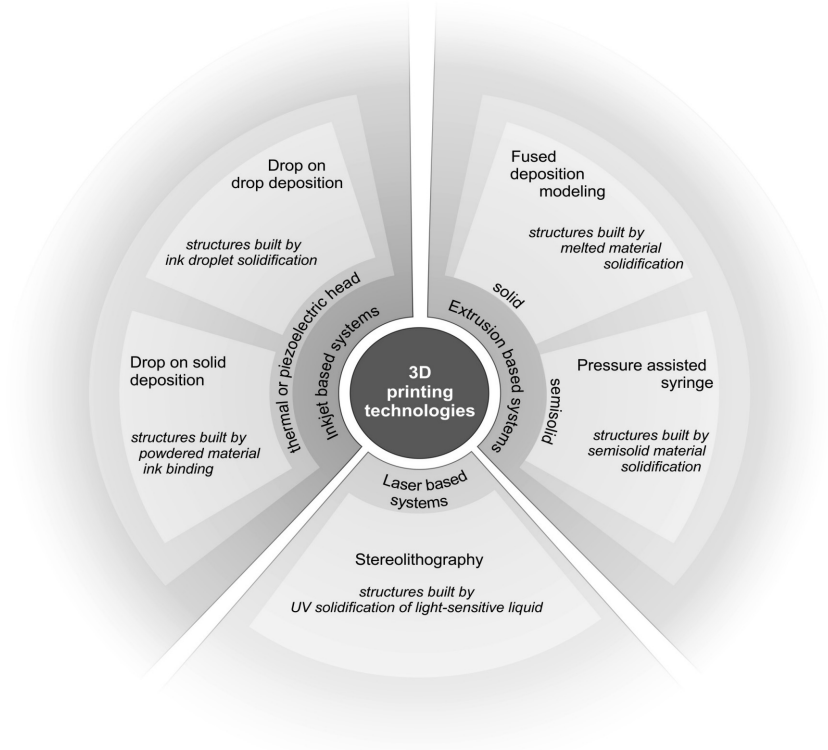

Figure 1. The development process of printing 3D model

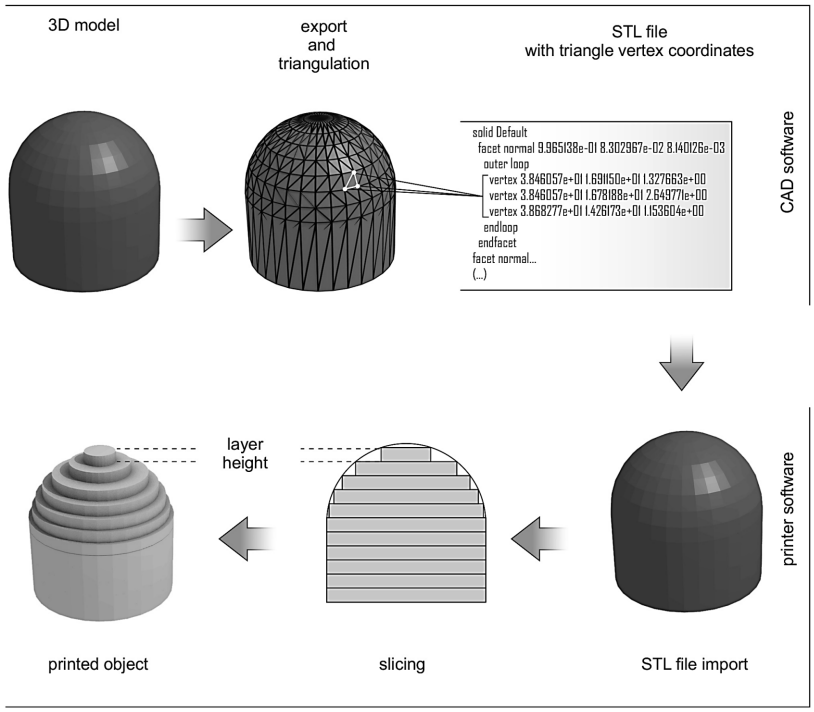

Figure 2. Diversity of 3D printing technologies

created with thermal or piezoelectric system (Fig. 3). In the case of thermal print heads, inks should be based on a volatile solvents, because heating resistor rapidly heats them in the chamber and growing bubbles of air generate the ink ejection force (6). In piezoelectric print heads, an electric pulse bends piezoelectric element and pushes out droplets of ink, which allows the usage of various types of inks (7). Active drug substance can be dissolved in ink or mixed with a powder bed. Powder properties (e.g., topology, particle size, porosity, wettability, reactivity with the ink), ink properties (e.g., viscosity, type of solvent, binding polymers) and process parameters (droplet size, spray rate) are essential for printed layer height and product properties.

In drop on drop (DoD) deposition method, droplets of ink solidify layer-by-layer on each other without powder addition (Fig. 3). Usually ink contains additives improving building properties e.g., polymers, waxes, suspensions. Unlike in DoS, layer height is smaller than droplet size and object could be printed with higher resolution (5).

The most precise 3D printing method is stereolithography, which involves polymerization of photopolymer in the presence of light (Fig. 4). A geometry of the object is transferred by the UV light at the surface of photoresin. Build platform is lowered and another layer is created. Its height depends on the light energy, resin properties and platform movement. The main weakness of this method is limited number of nontoxic resins and high energy of UV light which is commonly used (3, 4).

In the extrusion based system, APIs are mixed with polymers and object layers are built with the mixture continuously ejected through the nozzle (Fig. 5). Fused deposition modeling (FDM), also known as fused filament fabrication (FFF) is one of the rapid prototyping methods used in many different fields, in recent years also in pharmaceutical technology and medicine. The idea of this method is based on the application of successive layers of fused material by precisely controlled nozzle of the 3D printer. The thermoplastic polymer in the filament form of specified dimeter is used to construct the object. There is a variety of filaments commercially available, such as: ABS, PLA, PVA, Nylon etc. but only few of them can be applied in pharmaceutical development.

A schematic construction of FDM 3D printer is presented in Figure 4. The most important element of the system is printing head equipped with one or more nozzles that can be moved in two dimensions

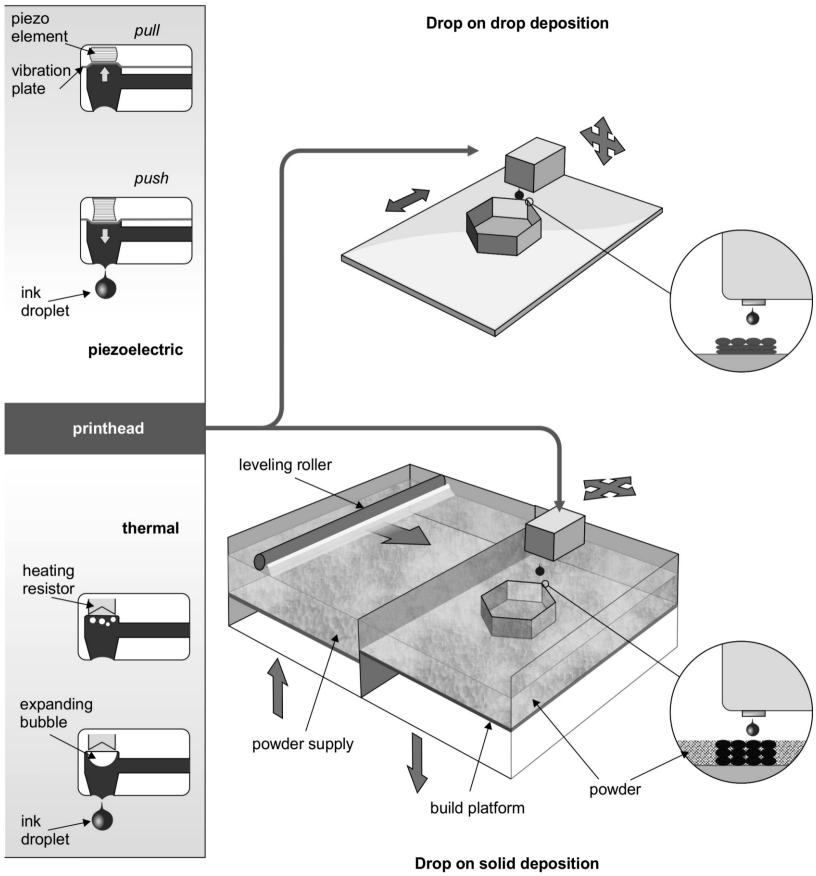

Figure 3. The printing mechanism with DoD and DoS printing methods

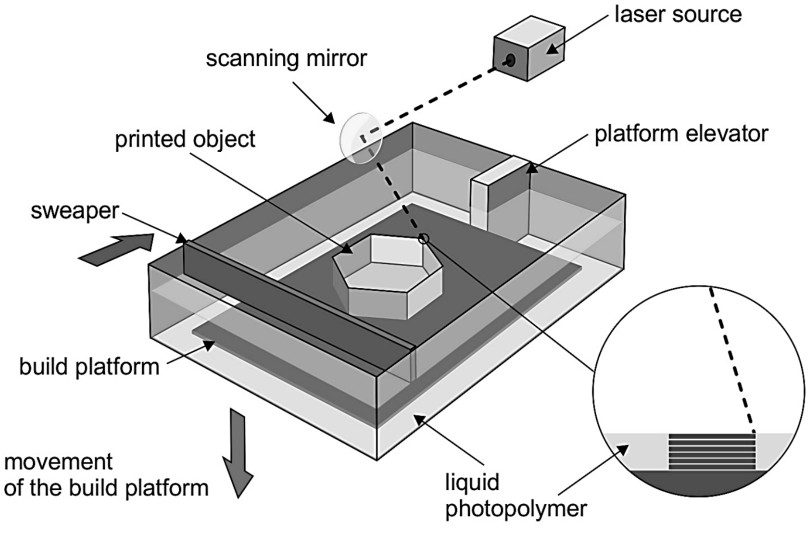

Figure 4. Stereolithographic printing system

e.g., along the y- and z-axes. The working temperature of nozzle is controlled in the wide range, because of different melting points of printing materials. Depending on the system, there can be one, two or even three nozzles attached to the printing head, which gives the opportunity to print with different materials varying in melting temperatures and physical properties such as water solubility. There are only a few companies offering printing heads containing one nozzle able to print with two materials with similar melting temperatures. The polymer materials are fused and mixed in the printing head with a fixed ratio and the printing is carried out with a combined material. The diameter of a standard nozzle is 0.4 mm, but in order to improve the quality of the printout, it can be exchanged to a smaller one, such as 0.3 mm or 0.2 mm. Another important element of the printer is the build platform (also called printing table) which should be capable to be heated, because some materials better stick to its surface when it is hot. The printing table is also movable in one, two or three axes depending on the system. Build platform in the presented 3D printer is moving along x-axis. In order to improve the polymer sticking to the table, it can be covered with a special texture tape BuildTak™. The printing space is limited by a minimum and maximum position of the nozzle tip within the 3 dimensions in relation to the printing table. Different FFF printers have opened or closed printing areas. The second ones are more suitable, especially for printing with polymers that are shrinking upon cooling.

There are many 3D printing process parameters that need to be considered. The temperature of the nozzle is dependent on the kind of a polymer and it should be set up near to its melting point, while printing table temperature depends on the material sticking properties. Printing speed have to be selected carefully depending on the used system, polymer, complexity of the printed object and expected quality of the printout. Typically 40 mm/s speed is used, but some printers can go up to 150 mm/s or even faster. Height of the layers generally affects the printing precision in the way, that the higher the layer is, the lower quality of the object will be. There are also some software parameters that have to be taken into consideration. The infill density is not so obvious parameter. During the object design, it seems to have a solid form but during the printing only the external walls, its bottom and top are solid. It is caused by filament material saving. The object can be printed with infill density from 0% to 100% which means that it can be empty or completely filled with material. The infill can also possess dif-

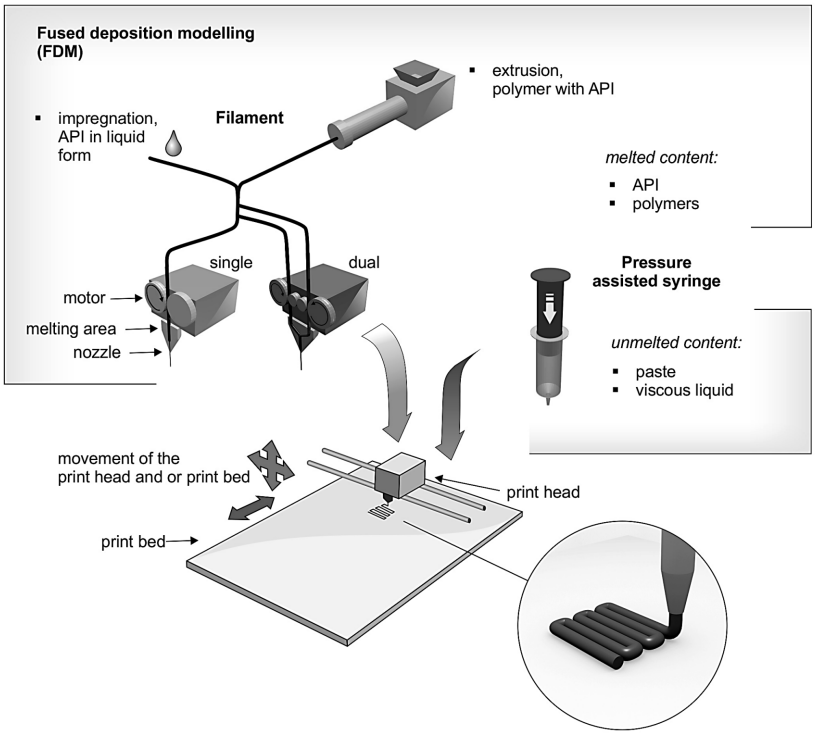

Figure 5. Fused deposition modeling – construction and mechanism of action

ferent geometries e.g., rectilinear or honeycomb. All of the parameters can affect the quality and properties of printed objects.

As previously mentioned, filaments that are available on the market have limited application in the pharmaceutical technology. Much more opportunities are given with fabrication of a specific filament by hot-melt extrusion in own laboratory. It allows to incorporate the API directly into the filament. It is also attractive method, because the process of hot-melt extrusion is well known in the pharmaceutical technology. This preparation method was utilized by Holländer et al. to produce poly(ε-caprolactone) (PCL) based filaments with incorporated indomethacin (8). Filaments with three different drug loading, i.e. 5%, 15% and 30% were prepared. It was stated that the amount of indomethacin in the filament significantly affected the properties of the filament, quality of the printed prototype and indomethacin release characteristics. Hot-melt extrusion was used also to produce polyvinyl alcohol (PVA) filament containing paracetamol (9) and ethylene vinyl acetate (EVA) filament with indomethacin (10).

Other alternative to introduce the drug into the polymer is impregnation of filament with API in the form of solution in volatile solvent (11). The impregnation of the PVA filament with a prednisolone methanolic solution resulted in the loading efficiency as low as 1.9%, and required application of organic solvents. It was also stated that despite that the prednisolone was in the amorphous state in the printed tablets, its dissolution was prolonged. The dissolution profiles were similar regardless of the dose of the API, and a quality of the tablets was evaluated according to the time after which more than 80% of the drug substance was released. Over 80% of prednisolone was dissolved from 3D printed tablets with 2 and 3 mg of API after 12 h and after 18 h from the tablets containing 4 – 10 mg of the active substance.

There is a great number of studies based on the non-pharmaceutical grades of filament material. Many of those are prepared from commercially available filaments shredded and re-extruded with the API or impregnated with it. That has to be highlighted, that the second extrusion of the same material could change its properties dramatically and that the filament material is not fully specified as it should be for pharmaceutical applications. Boetker et al. have combined a commercial filament with pharma grade hydroxypropyl methylcellulose in hot-melt extrusion process to modify the solubility of the material and improve the dissolution properties of the nitrofurantoin (12).

The additional advantage of this particular printing method, significant to drug manufacturing is simple control of the dose of the active substances by changing the volume of the designed drug form (11) or in some cases by modification of the infill ratio of the drug form. Usage of multi-nozzle 3D printers allows the production of drugs containing more than one active ingredient, also incompatible ones, which is a big advantage in the age of combined pharmaceuticals. A wide range of materials, that can be used for the preparation of 3D printing filament is available in pharmaceutical grade with different properties such as water solubility. A significant advantage is the possibility to obtain amorphous drug during a printing process, which allows to improve the dissolution characteristics of poorly soluble drugs. However, this matter has to be further fundamentally investigated due to the stability issues (13).

Overview of the latest research achievements

Current studies are focused on the application of 3D printing technology to the pharmaceutical dosage forms manufacturing, mostly solid oral dosage forms, such as conventional and modified-release tablets, implants, orodispersible tablets and films. The most commonly used printing techniques are based on the extrusion process (Table 1).

As for now, tablets are the most favored dosage form. In spite of it, poor patient compliance in drug administration leading to ineffective pharmacotherapy is stated. It could be changed by the development of different types of tablets in size, shape and design.

Many diseases, encountered particularly by geriatric patients, require therapy with a numerous active pharmaceutical ingredients administered separately. Incorporating several APIs into one dosage form may significantly improve patient compliance. 3D printing technique based on the room temperature extrusion process was utilized to obtain tablets named by authors “polypill”, containing captopril, nifedipine and glipizide characterized by different release mechanisms. A soft paste of each component of tablet, i.e., the API formulation feedstocks with different HPMC concentration, the tablet shell paste and the joining layer feedstock were prepared separately and extruded on a glass slide. The printed tablet was consisted of captopril osmotic pump, joining layer, nifedipine and glipizide in sustained release form (Fig. 6). Fast disintegration of joining layer allowed to split tablet into two separated parts with various release mechanism, captopril with zero order kinetic and nifedipine and glipizide with first

Table 1. Dosage forms prepared by 3D printing.

Dosage form	Active ingredient	Excipients	Ref.
3D printing			
	Fused deposition modeling (FDM)		
Caplet	Acetaminophen Caffeine	PVA filament	9
Caplet	Budesonide	PVA filament	14
Capsule	Acetaminophen	PLA filament, HPC, PEG 1500, polyvinyl alcohol-polyethylene glycol graft copolymer Brilliant Blue	15
Tablet	5-Aminosalicylic acid 4-Aminosalicylic acid	PVA filament, absolute ethanol	16
Tablet	Acetaminophen	PVA filament	17
Tablet	Fluorescein sodium	PVA filament, absolute ethanol	18
Implant	γ-Indomethacin	Ethylene vinyl acetate	10
T-shaped intrauterine systems	γ-Indomethacin	Ethylene vinyl acetate	10
Pressure assisted syringe			
Bilayer tablet	Guaifenesin	HPMC, poly(acrylic acid), microcrystalline cellulose, sodium starch glycolate	19
Tablet "polypill"	Aspirin Hydrochlorothiazide Atenolol Pravastatin sodium Ramipril	PVP, lactose, D-mannitol, sodium starch glycolate, HPMC, milli-Q purified water, cellulose acetate, PEG 6000, acetone, DMSO	20
Tablet "polypill"	Captopril Glipizide Nifedipine	HPMC, sodium chloride, D-mannitol, croscarmellose sodium, microcrystalline cellulose, sodium starch glycolate, PVP K30, tromethamine, cellulose acetate, PEG 6000, acetone, DMSO	21
Tablet	Theophylline	Ammonio methacrylate copolymer type A, ammonio methacrylate copolymer type B, HPC, triethyl citrate, triacetin	22
Drop on solid deposition			
Implant	Levofloxacin	Poly(L-lactic acid), ethanol, acetone	23
Implant	Rifampicin Isoniazid	Poly(DL-lactic acid), methanol, acetone, purified water	24
Tablet	Chlorpheniramine maleate	Microcystalline cellulose, basic butylated methacrylate copolymer, ammonio methacrylate copolymer type A, ethanol	25
Tablet	Diclofenac sodium	Microcrystalline cellulose, spray dried lactose, methacrylic acid - methyl methacrylate copolymer, ammonio methacrylate copolymer type A, PVP K25, methanol, acetone, ethanol	25
ODT	Acetaminophen	Colloidal silicon dioxide, PVP K30, lactose, mannitol, alizarin yellow	26
ODT	Levetiracetam	Colloidal silicon dioxide, glycerin, mannitol, microcrystalline cellulose, polysorbate 20, povidone, sucralose, butylated hydroxyanisole, and natural and artificial spearmint flavor	27
Drop on drop deposition			
Mucosal thin films	Cetirizine hydrochloride Diphenylhydramine hydrochloride Ibuprofen	Basic butylated methacrylate copolymer, ethanol	28

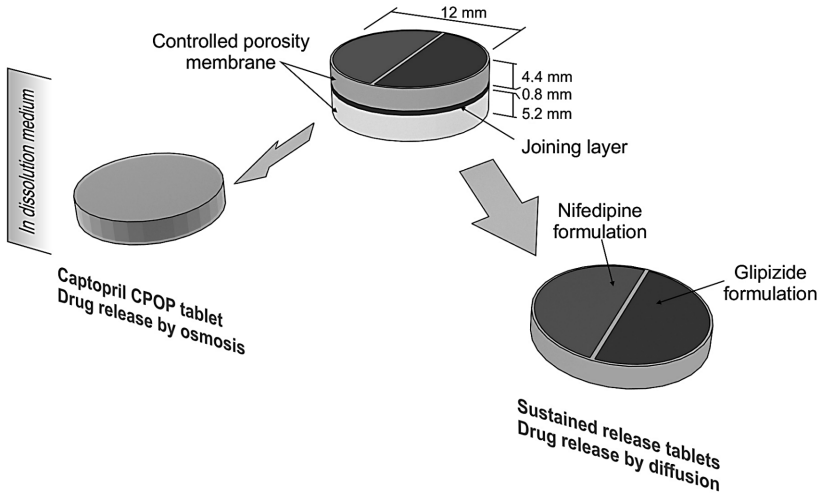

Figure 6. Schematic illustration of "polypill" tablet

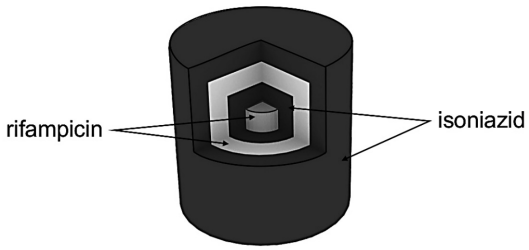

Figure 7. Schematic illustration of pulsed-release implant

order kinetic. The drug release rate was controlled by the amount of HPMC (21).

Modified-release budesonide caplets (rounded, hard capsule-shaped tablets) were fabricated using FDM 3DP, combined with hot melt extrusion (HME) and fluid bed coating. The PVA filament containing API was prepared through the grinding of the commercial PVA filament to obtain fine powder, mixing with budesonide and then extruding the mixture. Caplets with 9 mg of API were created with FDM 3D printer using previously prepared filament. Finally, printed caplets were coated with a solution of Eudragit® L100. The dissolution profile of 3D printed dosage form was compared with profiles of commercially available budesonide prolonged release tablets (Cortiment® 9 mg) and hard gelatin capsules containing gastro-resistant prolonged-release granules (Entocort® CR 3 mg). The dissolution test was performed in hydrochloric acid for 2 h and in phosphate buffer of pH changing during the test for further 8 h. All formulations were resistant to acidic condition, however their dissolution profiles were different. More than 90% of budesonide was released from Entocort® after 3 h, and 50% and over 80% of the drug after 10 h from Cortiment® and 3D printed caplets, respectively. Gradual drug release in intestinal environment, observed for printed caplets, indicated the possibility of application of printed form in intestinal inflammatory treatment (14).

Drop on solid deposition printing technique was used to fabricate pulsed-release implants in cylindrical shape, containing rifampicin and isoniazid used for treatment of bone tuberculosis. Powder of poly(DL-lactic acid) was used as a carrier material. It was solidified by binder solution of rifampicin or isoniazid to obtain alternating 4 layers of each drug from the center to periphery (Fig. 7). Drug release was evaluated using *in vitro* and *in vivo* tests ran for 8 weeks. Studies demonstrated that the dissolution profiles correlated with the data acquired during *in vivo* test performed with adult rabbits. In dissolution studies, peak values were obtained on the 2nd and 22nd day for isoniazid, whereas rifampicin was releasing slowly for the first 4 days, and maximum concentration was measured on the 10th and 34th day. Similar results were observed in *in vivo* studies. Maximum drug concentration (c_{max}) of isoniazid in bones was reached on the first and 21st day. In the case of rifampicin, no drug was released for the first 4 days, and c_{max} was detected as late as on the 14th and 35th day. Concentration of both drugs in arterial blood was very low, what indicated that they were distributed to the bones as a targeted place, and that side effects could be reduced (24).

Orally disintegrating dosage forms can overcome the swallowing problems encountered by patients with dysphagia.

In 2016 pharmaceutical company Aprecia has introduced Spritam® orodispersible tablets with levetiracetam that disintegrate in a matter of seconds when taken with a sip of liquid. They were produced with ZipDose® Technology platform featuring powder-liquid three dimensional printing method which allows manufacturing of highly porous drugs. Furthermore, ZipDose® enables to incorporate up to 1000 mg of active pharmaceutical ingredient and to effectively mask the unpleasant taste of a drug substance (27).

In recent years, orodispersible films have gained popularity, especially as a relevant dosage forms in therapy of pediatric, geriatric, handicapped or bedridden patients. The most commonly method used for ODFs preparation is solvent casting. However, formulation of fast dissolving films with rapid disintegration and good mechanical properties is still challenging. This issue may be solved by using one of the 2D printing technique in ODFs preparation, i.e. inkjet or flexography printing, where APIs solution or suspension is deposited onto a drug-free film (Table 2).

The influence of films preparation using inkjet printing and solvent casting methods on their properties were compared. PVA and carboxymethyl cellulose sodium salt (SCMC) at ratio 1 : 1 were used as a film forming polymers, and glycerol was added

Table 2. Application of 2D printing technique for films preparation.

Dosage form	Active ingredient	Excipients	Ref.
2D printing			
Inkjet printing			
ODF	Caffeine Loperamide hydrochloride	Propylene glycol, ethanol, purified water, edible icing sheets based on the corn starch, HPC, polyethylene terephthalate films	29
ODF	Clonidine hydrochloride	PVA, carboxymethylcellulose sodium, glycerol, methanol, absolute ethanol	30
ODF	Rasagiline mesylate	Propylene glycol, HPMC, crospovidone, glycerol, purified water	31
ODF	Salbutamol sulfate	Glycerine, purified water, commercial potato starch film,	32
ODF	Sodium picosulfate	Purified water, PEGylated poly(lactic-co-glycolic) acid, ethyl acetate, PVA, PEG 2000, PEG 3000, PEG 6000, ethanol, glycerol, pharmaceutical-grade oral film, hydrophobic non porous film, hydrophilic porous film	33
ODF	Piroxicam	PEG-400, ethanol, edible icing sheets based on the corn starch	34
Extended release film disodium	Dexamethasone-21-phosphate	DL-lactic/glycolic copolymer, PVA	35
Combining inkjet and flexographic printing			
Controlled release film	Propranolol hydrochloride Riboflavin sodium phosphate	Propylene glycol, glycerol, purified water, ethylcellulose, ethanol, alkyl ketene dimer-sized uncoated woodfree paper, triple-coated inkjet paper, double-coated sheet fed offset paper, water impermeable polyethylene terephthalate film	36
Controlled release film	Riboflavin sodium phosphate Propranolol hydrochloride Theophylline	Ethylcellulose, propylene glycol, glycerol, ethanol	37
Flexographic printing			
ODF	Indomethacin Itraconazole	Poloxamer 407, purified water, transparency film, rice sheet, rice paper	38
ODF	Piroxicam	PEG-400l, edible icing sheets based on the corn starch	34
ODF	Rasagiline mesylate Tadalafil	HPMC, crospovidone, glycerol, purified water, HPC, brilliant blue, ethanol	39

as a plasticizer. The casting solution was poured onto tray and dried in an oven at 30°C. Methanolic solution of clonidine hydrochloride and glycerol was printed onto earlier prepared free films to obtain final product – fast dissolving films containing from 7.6, to 250 μg of API per strip with dimension of 2 × 2 cm. ODFs with clonidine hydrochloride obtained in the solvent casting method were prepared by dissolving appropriate amount of API in PVA:SCMC solution, casting it onto tray, drying at 30°C and cutting into 4 cm^2 strips. The printed films had 4 times lower dose variation and better mechanical parameters than casted films. Films prepared with solvent casting method were brittle, which was indicated by the value of Young's modulus above 1000 MPa, while mechanical parameters of printed films were more related to placebo. ODFs containing 90 or 250 μg of clonidine hydrochloride per strip were evaluated after being exposed to the high temperature and humidity, i.e. 60°C and 75% RH or 30°C and 0-90% RH. In both cases, crystallization of API was detected only for films prepared by solvent casting method containing higher dose of drug substance. Furthermore, crystals growth was also observed in the case of casted films containing 90 μg of clonidine hydrochloride, subjected to higher humidity (30).

Flexographic printing technique was used to manufacture orodispersible films containing rasagiline mesylate or tadalafil. Substrate for printing, based on the HPMC was prepared by solvent casting method. The final placebo film was rolled up into jumbo roll and cut into daughter rolls with a diameter 2 cm x 100 m. An ink solution of rasagiline mesylate and an ink suspension of tadalafil were prepared by dissolving or dispersing APIs in ethanolic solution of HPC. Four layers of the ink solution or suspension with blue colorant were deposited onto free-drug film and cut into strips 3 cm length. ODFs with diameter 2 cm x 3 cm containing tadalafil or rasagiline mesylate were also prepared utilizing solvent casting method. ODFs prepared using printing technique as well as those prepared by casting method were flexible and did not break. Films containing rasagiline mesylate were smooth and crystallization was not observed regardless the method of their preparation. ODFs with tadalafil prepared by casting method were heterogeneous and large agglomerates and crystals were detected. Some crystals were also visible in the case of films produced with flexographic printing, but they were smaller and homogenously dispersed on the film surface. Orodispersible films prepared with casting method were characterized by higher drug concentration compared to the printed films, what indicated, that flexographic printing could be used only for manufacturing of ODFs containing low dose of high-potent drugs (39).

SUMMARY

The studies presented above, as well as other numerous researches on the 2D and 3D printing published in scientific journals during last years, are the clear evidence of the growing importance of these methods in different areas of medical sciences and in pharmaceutical technology. Its growing presence can be noticeable at the scientific congresses and in the increasing number of scientific publications during last years. At the 8th World Meeting on Pharmaceutics, Biopharmaceutics, and Pharmaceutical Technology, held in 2012 in Istanbul, Turkey, there was only one poster presentation on the 3D printing technology, one on the 2D printing, and one lecture describing application of inkjet printing in the drug technology. During the next meeting in 2014, there were two posters regarding this topics. However, in the same meeting held in the current year the 2D and 3D printing were among main hot topics of the event, and even the whole session on this topic was held, giving overall 6 lectures on 2D printing and 3 lectures on 3D printing. Poster sessions included 3 presentations on 2D printing and 4 posters on 3D printing. The recent researches in this area contained works on the different solid dosage forms preparation with fused deposition technology, its application in tissue bioengineering, inkjet printing as well as methods of preparation of filaments with active pharmaceutical ingredients, and qualification of 3D-printers for pharmaceutical applications.

The growing popularity of 2D and 3D printing is also noticeable in the remarkably increasing number of scientific papers published during last few years. Number of publications containing keyword "3D printing" that were registered in the Thomson Reuters Web of Science database grew from 165 in 2010 to 1336 in 2015. Among them 49, and 447, respectively, were related to the life sciences. No articles regarding application of 3D printing in the pharmacy were published in 2010, but in 2015 their number increased to 22. Similar results can be found for other keywords related to this topic, i.e. "fused deposition modeling", "fused filament fabrication" or "three dimensional printing". This demonstrates that the application of 2D- and 3D-printing technology to the area of pharmaceutical sciences is one of the most innovative directions of future researches

in the field, giving the new possibilities to the dosage form development and production.

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